AF

MS APPEAL BRIEF - PATENTS
PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of		Before the Board of Appeals	
Eiichi IISHI et al.		Appeal No.:	
Appl. No.:	09/697,329	Group:	1624
Filed:	October 27, 2000	Examiner:	HABTE, K.
Conf.:	8402		
For:	ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME		

APPEAL BRIEF TRANSMITTAL FORM

MS APPEAL BRIEF - PATENTS
Commissioner for Patents
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June 6, 2005

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Sir:

Transmitted herewith is an Appeal Brief on behalf of the Appellants in connection with the above-identified application.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. § 1.8.

A Notice of Appeal was filed on March 16, 2005.

☐ Applicant claims small entity status in accordance with 37 C.F.R. § 1.27

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Respectfully submitted,

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1422-0449P

Attachment(s)

PATENT
Attorney Docket: 1422-0449P

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APPEAL BRIEF ON BEHALF OF APPELLANT UNDER 37 C.F.R. § 41.37

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APPEAL BRIEF ON BEHALF OF APPELLANT UNDER 37 C.F.R. § 41.37

MS APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

June 6, 2005

Sir:

This is an Appeal from the Rejection of September 17, 2004 of claims 7 and 12-15 in the above-identified application.

I. REAL PARTY IN INTEREST

As evidenced by the Conveyance filed August 25, 2004 and recorded at Reel 11252, Frames 0362-0364 the Real Party In Interest in connection with the present application is the Assignee of record: SUMITOMO CHEMICAL COMPANY, LIMITED, 5-33 Kitahama 4-chome, Chuo-ku, Osaka, Japan.

II. RELATED APPEALS AND INTERFERENCES

There are no pending Appeals or Interferences related to the present application known to the Appellant or the Appellant's Legal Representatives.

III. STATUS OF CLAIMS

Claims 7 and 12-17 are pending in the application. Claims 7 and 12-15 stand rejected. Claims 16 and 17 have been allowed.

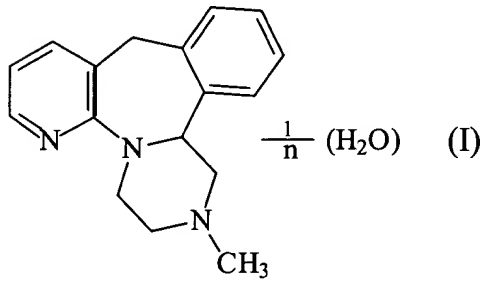
IV. STATUS OF AMENDMENTS

The only amendment filed after a Final Office Action in this application was filed September 1, 2004. However, as indicated in section "2" on page 2 of the September 17, 2004 Office Action, the Examiner withdrew the finality of the May 5, 2004 Office Action.

Accordingly, all amendments presented by the Appellant have been entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention as defined in independent claim 7 pertains to a crystal of an unlabeled mirtazapine hydrate represented by the formula (I):



(I)

wherein n is an integer of 1 to 5.

It is clear from disclosure in the specification that the present inventors had in their possession at the instant priority date an *"unlabeled"* mirtazapine hydrate. For example, the mirtazapine hydrate of the present invention is taught to be useful in the treatment of depression, see page 29, line 11 of the specification, and labeled compounds are not typically used in treatment regimens. Furthermore, the Preparation Example beginning at page 10, line 9 of the specification does not incorporate a labeled mirtazapine hydrate. Lastly, there is simply no teaching or suggestion in the specification that the mirtazapine hydrate should be labeled.

The mirtazapine hydrate of formula (I) is disclosed in the specification at page 3, lines 1-8.

Independent claim 16 has been allowed and is not involved in this appeal, and as such is not described here.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole issue presented for review is whether the combination of **Kaspersen et al.** (Journal of Label. Comp. and Radiopharm., Volume 27, No. 9, page 1055, 1989) and **Khankari et al.** (Thermochemica Acta 248 (1995), pages 61-79) suggests all the elements of claims 7 and 12-15 to support an obviousness rejection under 35 U.S.C. § 103(a).

VII. ARGUMENT

Kaspersen et al. and Khankari et al. fail to suggest all of the elements set forth in claims 7 and 12-15 to properly support a rejection under 35 U.S.C. §103(a).

A. The Present Invention and its Advantages

Mirtazapine has been sold as a pharmaceutical useful as an antidepressant in many countries including the United States. It is apparent from the whole disclosure of the instant specification that the object of the present invention is to provide pharmaceuticals useful as an antidepressant for

therapeutic applications (see, *inter alia*, page 1, lines 11-15 of the instant specification). In other words, the ultimate object of the present invention is to provide low hygroscopic crystals of mirtazapine useful as therapeutic agents, which are prepared by drying the crystals of a mirtazapine hydrate of inventive formula (I).

Accordingly, the crystals of a mirtazapine hydrate of inventive formula (I) are well suited as an intermediate for the antidepressant therapeutic agent, which are low hygroscopic crystals of mirtazapine.

B. Distinctions of the Invention Over Kaspersen et al. and Khankari et al.

When a rejection is based on 35 USC §103, what is in issue in such a rejection is "the invention as a whole," not just a few features of the claimed invention. Under 35 U.S.C. §103, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The determination under §103 is whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. See In re O'Farrell, 853 F.2d 894, 902, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). In determining obviousness, the invention must be considered as a whole and the claims must

be considered in their entirety. See Medtronic, Inc. v. Cardiac Pacemakers, Inc., 721 F.2d 1563, 1567, 220 USPQ 97, 101 (Fed. Cir. 1983).

In rejecting claims under 35 USC 103, it is incumbent on the examiner to establish a factual basis to support the legal conclusion of obviousness. See, In re Fine, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In so doing, the examiner is expected to make the factual determinations set forth in Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), and to provide a reason why one of ordinary skill in the pertinent art would have been led to modify the prior art or to combine prior art references to arrive at the claimed invention. Such reasoning must stem from some teaching, suggestion or implication in the prior art as a whole or knowledge generally available to one having ordinary skill in the art. Uniroyal Inc. v. F-Wiley Corp., 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988), cert. denied, 488 U.S. 825 (1988); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 293, 227 USPQ 657, 664 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986); ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). These showings by the examiner are an essential part of complying with the burden of presenting a *prima facie* case of obviousness. Note, In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious

unless the prior art suggested the desirability of the modification. In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992).

Kaspersen et al. disclose the preparation of certain labeled mirtazapine compounds for metabolic studies. For example, the compound at page 1058, Fig. 4, which is identified by the Examiner as being particularly relevant, is abbreviated as "[$^{13}C_6$]-Org 3770" and denoted as compound "1c". Also, the compound at page 1067 is abbreviated as "[10-^{14}C]-Org 3770" and is denoted as compound "1d".

The Examiner argues that the presently claimed hydrated form of **un**labeled mirtazapine is obvious, since: 1) Kaspersen et al. **inherently** form the hydrated form of the labeled mirtazapine; and 2) based on the teachings of Kaspersen et al., it would be obvious to the skilled artisan to remove the radiolabel from the labeled mirtazapine hydrate of Kaspersen et al. to form the **un**labeled mirtazapine hydrate for ***pharmaceutical purposes***. Appellants respectfully disagree with the Examiner that Kaspersen et al. **inherently** form the hydrated form of the labeled mirtazapine. Also, in light of the above-described requirements for a determination of obviousness, Appellants respectfully find that Kaspersen et al., when taken alone or in combination with Khankari et al., do not make the presently claimed hydrated form of **un**labeled mirtazapine obvious.

Appellants now focus on the Examiner's finding of inherency.

During prosecution, Appellants set forth the position that one skilled in the art would not find it obvious that the labeled compounds of Kaspersen et al. inherently are formed as a hydrate as presently claimed. Beginning at page 4, line 6 of the September 17, 2004 Office Action, the Examiner states:

> The examiner disagrees with applicants. Both applicants and Kaspersen use an extremely similar method, thus, it is presumed that the same hydrate product is formed from virtually the same crystallization method. Kaspersen et al. on page 1066 teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound 1c) from the crude product using charcoal, methanol/water solvent mixture to achieve colorless crystals. Applicants on page 6 (lines 5-6) also discloses mixed solvents such as methanol/water, plus charcoal to make crystals of a mirtazapine hydrates. The only difference between applicant's mirtazapine and Kaspersen's Org-3770 is that Kaspersen's compound 1c is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. One skilled in the art would presume that labeled and unlabelled would crystallize in the same way.

Appellants respectfully submit that the skilled artisan would not reasonably conclude that the labeled compounds of Kaspersen et al. would form a hydrate in the experimental workup of Kaspersen et al. as asserted by the Examiner. In the workup for compound 1c of Kaspersen et al., it is clear that Kaspersen et al. do not believe that the final product is a hydrate. Kaspersen et al. teach that: "[n]o impurities were detectable", see page 1066, lines 7-8. Since the goal was to make mirtazapine, any water present would have been considered as an impurity. For instance, the peaks associated with

the IR-spectrum described by Kaspersen et al. do not include a peak around 3000 cm^{-1} as is typically associated with the O-H stretching vibration in water.

In response to this argument, the Examiner states (in the last three lines of page 7 of the September 17, 2004 Office Action):

> The examiner disagrees with applicants. First of all, the presence of water would not be spotted using TLC, HPLC or GC methods.

Appellants respectfully disagree. Kaspersen et al. would have at their disposal, the data relating to the anhydrous mirtazapine compounds as described in the reference cited in footnote "1" in the Introduction section. It is reasonable to conclude that Kaspersen et al. would be able to discern whether a hydrate was formed in their workup using TLC, HPLC or GC methods based on comparing their retention times to the retention times described in the reference cited in footnote "1" in the Introduction section.

Also, the characterization of the compounds of Kaspersen et al. includes IR and NMR techniques, which Khankari et al. teach readily show water peaks. This is evidenced by Khankari et al. at Fig. 9 on page 74, wherein Khankari et al. teach that IR and solution NMR are used to test for hydrates.

With respect to the IR technique for measuring hydrates, Fig. 1 of the present application shows how clearly the O-H stretching vibration shows at ~3000 cm^{-1}. It is reasonable to presume that for accuracy sake, Kaspersen et al. would report this peak associated with water if Kaspersen et al. in fact made the mirtazapine hydrate as asserted by the Examiner.

With respect to NMR techniques for identifying hydrates, Appellants turn to Fig. 10 on page 76 of Khankari et al., wherein Khankari et al. show how readily discernible the dihydrate form of carbamazepine is using C^{13} NMR. Fig. 10 is reproduced herein:

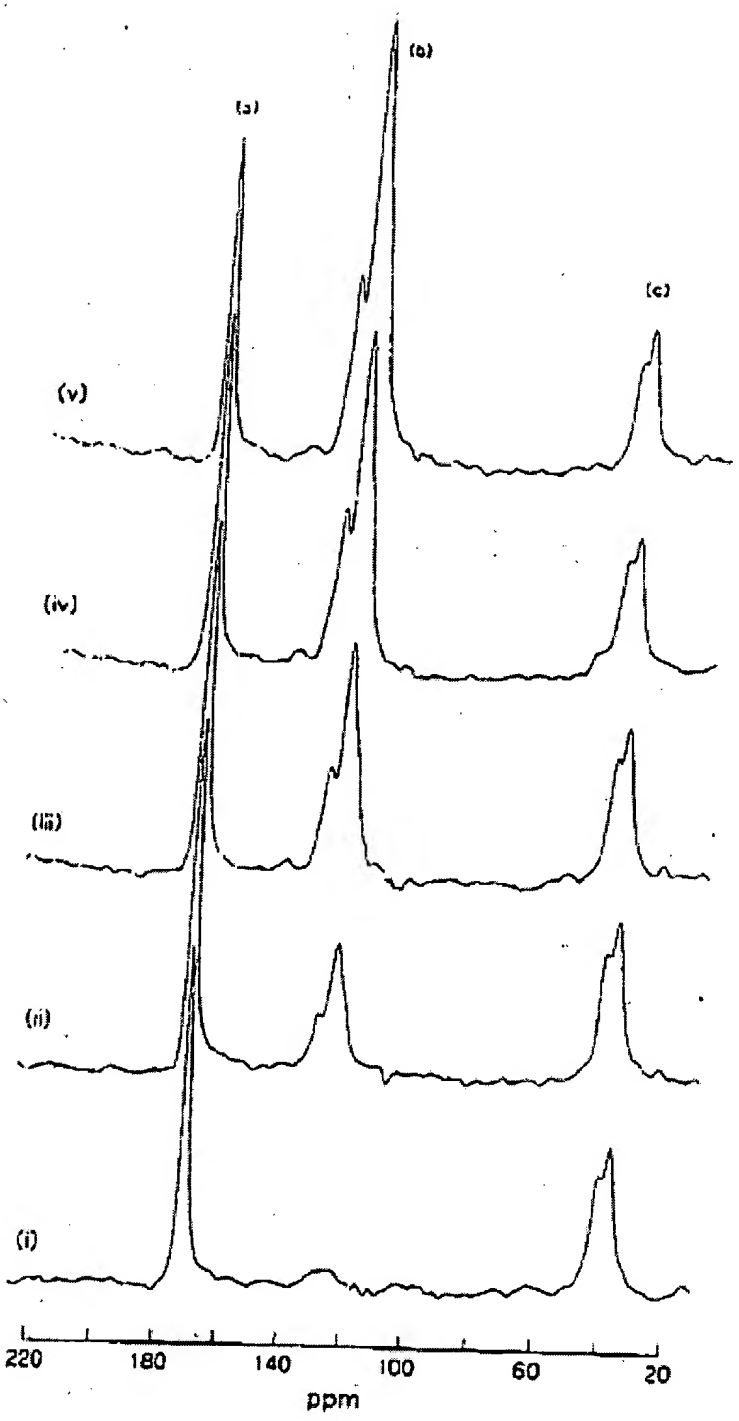


Fig. 10. ^{13}C spectra of mixtures of carbamazepine anhydrate (I), carbamazepine dihydrate (II) and glycine. The peak assignments are (a) the carbonyl carbon of glycine, (b) all carbons of II, and (c) the α-carbon of glycine. The mole fraction of II in the mixtures increases from spectrum (i) to spectrum (v) (Reproduced from Ref. [63] with the permission of the copyright owner, Plenum Publishing Corporation, New York, USA.)

In the above figure, it is easy to recognize the carbamazepine dihydrate (II) peaks labeled as "(b)" at ~125ppm as the concentration of the dihydrate increases from spectrum (i) to spectrum (v) with respect to the concentration of the anhydrate. Accordingly, it is reasonable to presume that for accuracy sake, Kaspersen et al. would identify and report that the labeled compound [10-^{14}C]-Org 3770 is a hydrate in the ^{13}C NMR of Fig. 9 on page 1061, **if** Kaspersen et al. in fact made the mirtazapine hydrate as asserted by the Examiner.

The Examiner bases his finding that the compound 1c of Kaspersen et al. ***inherently*** forms a hydrate in the fact that the product was purified in a methanol/water solvent as described in the following disclosure in the first paragraph on page 1066 of Kaspersen et al.:

> "The product was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3; v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colorless crystals, m.p. 123, 8-125, 8°C. No impurities were detectable either on TLC, HPLC or GC."

The Examiner asserts that this workup is sufficiently similar to the workup described in the present specification that one skilled in the art would assume that the mirtazapine final product of Kaspersen et al. is a hydrate, as presently claimed.

However, as stated above, the assumption that a hydrate is formed using the recrystallization technique of Kaspersen et al. is not tenable. It is clear upon a review of Inventive Examples 1, 6, 8 and 11 that there are striking dissimilarities between certain embodiments of the present invention and the recrystallization technique of Kaspersen et al. In both Inventive Examples 1 and 6, the present inventors teach that the mirtazapine is exposed to water by adding a thin stream of water to the solution of dissolved mirtazapine. This solution was cooled until the mirtazapine hydrate crystals crashed out. Also, in Examples 8 and 11, seed crystals of the mirtazapine hydrate were added to the dissolved mirtazapine. None of these steps have been performed by Kaspersen et al. Accordingly, the Examiner has not established that Kaspersen et al. teach a process, which inherently forms the mirtazapine hydrate, as presently claimed.

In response to this argument, the Examiner states (in the paragraph bridging pages 4-5 of the September 17, 2004 Office Action):

> In regard to applicant's argument that the processes of making hydrates (see Inventive Examples 1, 6, 8 and 11) are different from that of Kaspersen's, the examiner disagrees with applicants. This is a speculation. Whether a thin stream of water is added to the solution or the water is part of the water/methanol mixture in crystallizing the mirtazapine, it makes no difference in making hydrates.

Appellants respectfully submit that it is the Examiner who is improperly speculating. In rejecting claims under 35 USC 103, it is incumbent on the

examiner to establish a factual basis to support the legal conclusion of obviousness. See, In re Fine, *supra*. Appellants are merely pointing out that the basis upon which the Examiner supports his legal conclusion of obviousness is not solid.

In addition, even assuming *arguendo* that a hydrate is obtained when the compound of Kaspersen et al. is crystallized from a mixed solvent of water and an alcohol, it cannot be predicted from Kaspersen et al. whether a solvate with an alcohol or a hydrate would be obtained, when an unlabelled compound which is different from the labeled compounds disclosed by Kaspersen et al. is crystallized from a mixed solvent of water and an alcohol by a method as disclosed in the present specification.

Based on the foregoing, it is improper for the Examiner to conclude that Kaspersen et al. inherently form the labeled mirtazapine hydrate simply because water is used in the workup.

Even assuming *arguendo* that Kaspersen et al. inherently form the labeled mirtazapine hydrate, Appellants respectfully disagree with the Examiner's finding that it would be obvious to the skilled artisan to remove the radiolabel from the labeled mirtazapine hydrate of Kaspersen et al. to form the **un**labeled mirtazapine hydrate for ***pharmaceutical purposes***.

As noted above, it is Appellant's position that the Kaspersen et al. would have reported the water peak associated with the hydrate in the IR spectrum if

it had been present. In response to Appellant's position, the Examiner states (see page 8, beginning at line 6 of the September 17, 2004 Office Action):

> The IR peaks reported by Kaspersen et al. does not necessarily show a complete spectrum of the labeled mirtazapine compound. Thus, it is incorrect to use the only 4 peaks reported by Kaspersen as the only peaks for the molecule. It is presumed that these peaks are the only important ones for the sake of the report, but not the "only" peaks for the molecule. In fact, in many IR data reports only important peaks are reported and usually peaks from water or other weak peaks are ignored. The peaks are not usually reported because they are very broad or they are not important because they are not part of molecule. Thus, applicant's argument that the IR-spectrum described by Kaspersen et al. do not include a peak around 300 cm^{-1} is not persuasive. Additionally, the examiner is providing six US Patents (5,284,857; 5,401,753; 5,397,790; 5,583,149; 4,524,146 and 5,468,768) as an evidence to rebut applicant's argument.

This argument presented by the Examiner goes against the foundation of the Examiner's finding of obviousness. The Examiner argues that Kaspersen et al. inherently form the hydrated form of the labeled mirtazapine and that it would be obvious to the skilled artisan to form the **un**labeled hydrate for ***pharmaceutical purposes***. However, the fact that Kaspersen et al. do not report the water peak associated with the hydrate, would lead the skilled artisan to believe that the **anhydrous form** was actually used in the metabolic studies. Accordingly, there would be no motivation to use the hydrated form of the **un**labeled compound for ***pharmaceutical purposes***.

In addition, the skilled artisan would be reluctant to hydrate the apparently anhydrous form of mirtazapine of Kaspersen et al. for

pharmaceutical purposes in view of the teachings of Khankari et al.. Khankari et al. teach (at page 77, lines 2-5 from the bottom) that "hydration or dehydration of a pharmaceutical solid during formulation development or in a final dosage form may adversely affect the physical, chemical and/or biological performance of the pharmaceutical product." Accordingly, there would be no motivation for the skilled artisan to hydrate the apparently anhydrous form of mirtazapine of Kaspersen et al. as an **un**labeled compound for ***pharmaceutical purposes***. Accordingly, the Examiner's determination under §103 that the claimed invention is obvious improperly ignores the requirement that the invention as a whole must be considered as seen through the eyes of a person of ordinary skill in the art at the time the invention was made. See In re O'Farrell, *supra*.

Kaspersen et al. disclose that these compounds are labeled because:

> "[f]or metabolic studies in animal and man and for the determination of the bioavailability, the compound labeled with ^{3}H, ^{14}C, and ^{13}C was needed."

Thus, it is an object of Kaspersen et al. to prepare only labeled compounds (see page 1055, item "INTRODUCTION"), and not unlabelled compounds, as presently claimed. In other words, the skilled artisan would reasonably conclude that the labeled compounds prepared by Kaspersen et al. are to be administered a single time for studies.

In conclusion, the Examiner states:

> Note that obviousness can be for any purpose. Here, since unlabeled mirtazapine is known pharmaceutical, its unlabeled hydrate can be obvious for pharmaceutical purposes, even if it is not obvious for metabolic studies.

Here the Examiner seems to have dropped the assertion that Kaspersen et al. inherently teach mirtazapine hydrate. The Examiner seems to be making a broader statement that it would be obvious to modify any anhydrous compound having a pharmaceutical application, to be in the hydrate form with the reasonable expectation that the hydrated compound would still be useful in the same pharmaceutical application. Appellants respectfully disagree with the Examiner's broad statement.

The courts have consistently required that a *prima facie* case of obviousness can be made by modifying or combining prior art as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In In re Merck & Co., Inc., the claims were directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) and were rejected as *prima facie* obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological

properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant.

Here, there is no such evidence of record supporting the Examiner's assertion that there would be a reasonable expectation of success that modifying the anhydrous form of mirtazapine to be in the hydrated form would result in a compound useful in pharmaceutical applications.

For example, Khankari et al. teach at page 70, first paragraph that theophylline and carbamazepine give "erratic bioavailability" upon formation of the hydrate. Also, on page 71, third paragraph, Khankari et al. teach that the hydrate form of dihydrophenylalanine is more sensitive to oxidation than the anhydrous form. Lastly, Khankari et al. teach at page 72, third paragraph that the anticonvulsant drug carbamazepine "can lose up to one third of its effectiveness when stored in humid conditions."

In view of the fact that the prior art teaches that modifying anhydrous forms of pharmaceutical compounds to be in the hydrate form, can have negative effects on the properties of the pharmaceutical compounds, Appellants respectfully submit that without a specific teaching directed towards the improved effects of forming the hydrated form of mirtazapine in pharmaceutical applications, the skilled artisan **would not reasonably expect** that modifying the anhydrous form of mirtazapine to be in the hydrate form would give a compound useful in the same pharmaceutical application.

In view of foregoing, Appellants respectfully submit that there are significant patentable distinctions between the present invention and the teachings of Kaspersen et al. when taken in combination with Khankari et al.

VIII. CONCLUSION

The Appellant has demonstrated that the Examiner has failed to successfully allege that the rejected claims are *prima facie* obvious. For the reasons advanced above, it is respectfully submitted that all claims in this application are allowable. Thus, favorable reconsideration and reversal of the Examiner's rejection of claims 7 and 12-15 under 35 U.S.C. §103(a), by the Honorable Board of Patent Appeals and Interferences, are respectfully solicited.

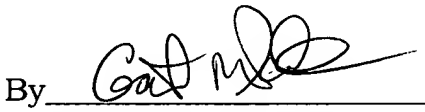
The required Appeal Brief fee in the amount of $500.00 is attached hereto.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for filing a response in connection with the present application. The required fee of $120.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH &, BIRCH, LLP

By 
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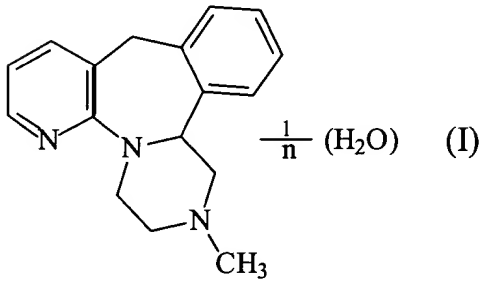
Attachment: 1) CLAIMS APPENDIX
2) EVIDENCE APPENDIX
3) RELATED PROCEEDINGS APPENDIX

CLAIMS APPENDIX

1-6. (Canceled)

7. (Previously Presented) A crystal of an unlabeled mirtazapine hydrate represented by the formula (I):



$\frac{1}{n}(H_2O)$ (I)

wherein n is an integer of 1 to 5.

8-11. (Canceled)

12. (Previously Presented) The crystal of a mirtazapine hydrate according to claim 7, wherein the average particle diameter of the crystals is 60 to 150 μm.

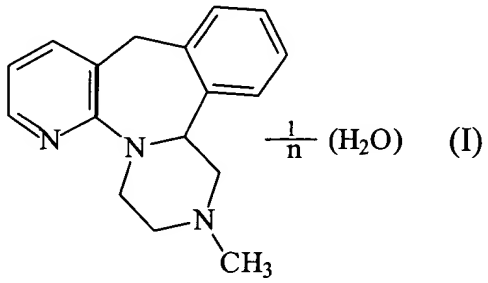
13. (Previously Presented) The crystal of a mirtazapine hydrate according to claim 7, wherein the crystal is pulverized.

14. (Previously Presented) The crystal of a mirtazapine hydrate according to claim 13, wherein the average particle diameter of the pulverized crystals is 10 to 70 μm.

15. (Previously Presented) The crystal of a mirtazapine hydrate according to claim 13, wherein the average particle diameter of the pulverized crystals is 20 to 60 μm.

16. (Previously Presented) A method for treating a human suffering from depression, comprising administering a pharmaceutically acceptable composition prepared from an effective amount of mirtazapine crystals having a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours.

17. (Previously Presented) The method according to claim 16, wherein the mirtazapine crystals have been prepared by a process comprising drying crystals of a mirtazapine hydrate represented by the formula I:



(I)

wherein n is an integer of 1 to 5.

EVIDENCE APPENDIX

Not Applicable - None

RELATED PROCEEDINGS APPENDIX

Not Applicable – None